(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 June 2003 (19.06.2003)

PCT

(10) International Publication Number
WO 03/050237 A2

(51) International Patent Classification[7]: C12N

(21) International Application Number: PCT/US02/32096

(22) International Filing Date: 9 October 2002 (09.10.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/339,294 12 December 2001 (12.12.2001) US

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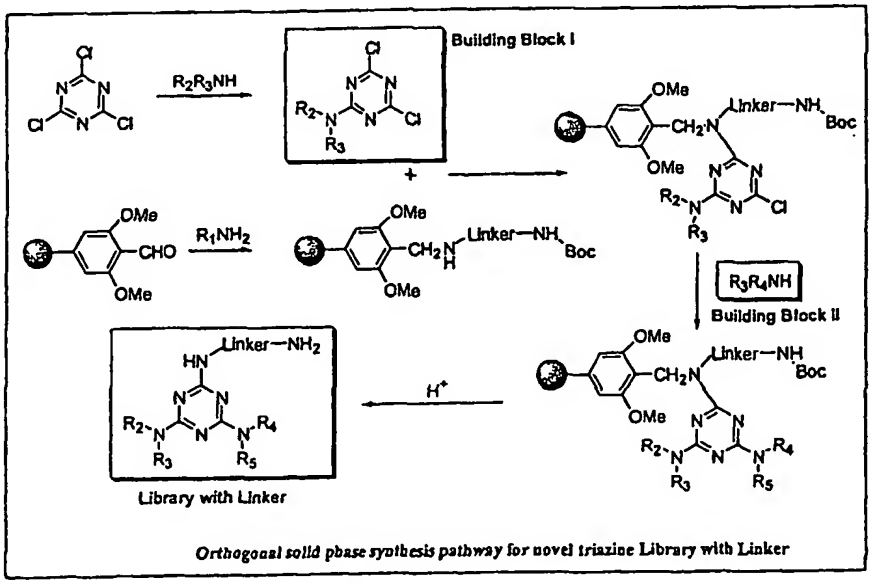
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: TRIAZINE LIBRARY WITH LINKERS



Orthogonal solid phase synthesis pathway for novel triazine Library with Linker

(57) Abstract: Triazine linkers can be used as universal small molecule chips for functional proteomics and sensors. These compounds are prepared by making a first building block by adding a first amine by reductive amination of triazine, making a second building block by adding a second amine to cyanuric chloride, and combining the first and second building blocks by aminating the first building block onto one of the chloride positions of the second building block.

WO 03/050237 A2

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

TRIAZINE LIBRARY WITH LINKERS

Field of the Invention

[0001] The present invention relates to triazine linkers which can be used as universal small molecule chips for functional proteomics and sensors.

Background of the Invention

[0002] The Human Genome Project provided a huge amount of sequence data for dozens of thousands of genes. Elucidating the function of each gene (so-called functional genomics) is the next step in the challenge of understanding human genetics[1]. Conventionally, geneticists have investigated the function of unknown genes by comparing normal phenotypes with knock-out or over-expression of the target gene, based on the assumption that the phenotypic difference is closely related to the function of the target gene. Recent developments in RNAi[2] and antisense techniques[3] have make it possible to temporarily turn off given gene expression by targeting mRNA rather than the DNA genome itself.

[0003] A novel approach using chemical library screening to find an interesting phenotypic change by targeting specific gene products, that is, proteins, has emerged as an alternative tactic; this is called chemical genetics[4]. In chemical genetics, one chemical compound may specifically inhibit or activate one target protein (for purposes of illustration, called "protein A"). Thus, the compound is equivalent to the gene knock-out or over-expression of the corresponding gene A, as in conventional genetics.

[0004] Combinatorial library techniques[5] facilitate the synthesis of many molecules. These techniques can be combined with high throughput screening (HTS) to screen many compounds to discover a novel, small molecule in the first step of chemical genetics study. Once one finds an intriguing small molecule, here referred to as "molecule A", that induces a novel phenotype in cells or in an embryonic system, the next

step is to identify the target protein and the biochemical pathways involved. An affinity matrix on bead or a tagged molecule (photoaffinity, chemical affinity, biotin or fluorescence) obtained by modifying molecule A, is commonly used for identifying the target protein. The target can be fished out by binding affinity of the proteins to the immobilized molecule, followed by separation on gel and sequencing by tandem mass spectrometry (MS-MS) technique. As the affinity matrix isolation usually gives multiple proteins, including non-specific binders, it is best to compare the gel results with those of control matrices side by side. Desirable control matrices will be obtained from structurally similar, molecules to molecule A which are inactive. The proteins that bind only to the active affinity matrix, without binding to the control matrices, are promising target candidates. The candidate proteins are then purified and screened *in vitro* with molecule A to confirm that the isolated protein is truly protein A.

[0005] As a whole, successful chemical genetics work will identify a novel gene product (*i.e.*, protein A), and its on or off switch, small molecule pairs. By analyzing the phenotype change, the function of protein A, which is the expression product of gene A, will be discerned. At the same time, the identified small molecule key, molecule A, is a useful biochemical tool to regulate the pathway of protein A, and may be a promising drug candidate as well.

[0006] Unfortunately, the current approach of chemical genetics intrinsically contains a very difficult step, that of modifying molecule A into an affinity molecule. In order to add a linker to molecule A without adversely affecting its activity, a thorough structure-activity relationship (SAR) study of molecule A is required to find a proper site for linker addition. This site is probably a site of molecule A exposed to the solvent direction from a binding pocket in

protein A. This procedure is, in many cases, extremely cumbersome, and sometimes is even completely impossible.

Summary of Invention

[0007] It is an object of the present invention to overcome the aforesaid deficiencies in the prior art.

[0008] It is another object of the present invention to provide an improved method for chemical genetics.

[0009] It is a further object of the present invention to synthesize linker libraries by combinatorial methods for screening in phenotypic assays.

[0010] The present invention comprises a method for chemical genetics using library molecules carrying a linker (LL: library with linker) from the first step of the procedure. In this method, LL is synthesized by combinatorial methods and screened in phenotypic assays. The selected active compounds are directly linked to resin beads or to a tagging moiety without further SAR study using the already existing linker. Eliminating the requirement for structure-activity relationship determination dramatically accelerates the connection of function screening to the affinity matrix step. This reduces the assay time from months to days, making the chemical genetics approach much more practical and powerful than it has been heretofore.

Brief Description of Drawings

[0011] Figure 1 shows examples of triazine-linker compounds.

[0012] Figure 2 shows a conventional synthetic pathway of triazine library by solution chemistry.

[0013] Figure 3 shows an orthogonal solid phase synthesis pathway for the triazine library with linker according to the present invention.

[0014] Figure 4 illustrates synthesis of building blocks according to the present invention.

[0015] Figure 5 shows syntheses of triazine compound with linker.

[0016] Figure 6 illustrates agarose bead synthesis of the triazine derivatives of the present invention.

Detailed Description of the Invention

[0017] Triazine is used as the linker library scaffold. Triazines are used because they are structurally similar to purine and pyrimidine, and they have demonstrated their biological potentials in many applications. In particular, triazines have many drug-like properties, including molecular weight of less than 500, cLogP of less than 5, etc. As the triazine scaffold has three-fold symmetry, the modification is also highly flexible and able to generate diversity. Furthermore, the startng material, triazine trichloride, and all of the required building blocks, which are amines, are relatively inexpensive. Because if its ease of manipulation and the low price of the starting material, triazine has elicited much interest as an ideal scaffold for a combinatorial library, resulting in several triazine libraries having been published in the literature[7]. However, all of the reported library synthesis procedures, both for solid and solution phase chemistry, are based on sequential aminations using the reactivity differences of the three reaction sites. This is shown in Figure 2, the conventional synthetic pathway of a triazine library by solution chemistry.

[0018] In this conventional method, the first substitution occurs at low temperatures while the second and third reactions require subsequently higher temperatures. This stepwise amination approach, however, is difficult to generalize for nucleophiles having differing reactivities. Thus, they may generate many byproducts together with the desired product.

[0019] The present invention solves the problem of byproducts using a straightforward synthetic pathway that can

be used for the general preparation of a trisubstituted triazine library. The process of the present invention does not use selective amination, which requires careful monitoring of the reaction and purification steps. Instead, the present process uses three different kinds of building blocks to construct the library. The first amine (linker) is loaded onto an acid-labile aldehyde resin substrate such as by reductive amination mono- or di-methoxybenzaldehyde resins. The second amine is then added to cyanuric chloride to form a building bock with the dichlorotriazine core structure. These two building blocks are then combined by amination of the first building block onto one of the chloride positions of the second building block. Any sequential over-amination on the other chloride position is efficiently suppressed by physical segregation from any other amine available on the solid support. The third building block, which can be a primary or secondary amine, then reacts with the last chloride position to produce the trisubstituted triazine. Since all reactions are orthogonal to each other, no further purification is required after cleavage of the final compound, as shown in Figure 3. Using this established synthetic scheme, a linker was introduced in the trisubstituted triazine library to synthesize thousands of library linker compounds in amounts of about 1-2 mg.

Syntheses of building blocks

[0020] To a solution of 100 mg (0.543 mmole) cyanuric chloride, purchased from A cross Chemical Company, USA, and 0.05 ml DIEA, purchased from Aldrich Chemical Company, USA, in 5 ml anhydrous THF, purchased from Aldrich Chemical Company, USA, was added each amine or alcohol reagent (0.652 mmol, or 1.2 eq) at 0°C. The reaction mixture was stirred for 30 minutes at 0°C. After TLC checking, the reaction mixture was filtered and the solvent removed *in vacuo*. The compounds were

purified by column chromatography. Each compound was identified by LC-MS (Agilent 1100 model). This scheme is shown in Figure 4, and the identification of the building blocks is shown in Table 1.

Table 1. Identification of Building Blocks (A1-Y1)

The products were identified LC-MS (Agilent 1100 model)

Comp. ID	Mass (m+1)	Comp. ID	Mass (m+1)	Comp. ID	Mass (m+1)
A1	235	J1	289	S1	285
B1	205	K1	221	T1	242
C1	219	L1	269	U1	206
D1	359	M1	255	V1	208
E1	299	N1	256	W1	332
F1	207	O1	249	X1	222
G1	273	P1	315	Y1	180
H1	235	Q1	241		
11	233	R1	291		

Syntheses of triazine library with linker

[0021] To a solution of 1.0 g (1.1 mmole) PAL™-aldehyde resin, purchased from Midwest Bio-Tech, USA, was added 1.5 g (3.5 mmole) of Boc-linker (2-[2-amino-ethoxy-ethoxyethyl]-carbamic *tert*-butyl ester) in 50 ml anhydrous THF containing 10 ml of acetic acid at room temperature. The reaction mixture was stirred for one minute at room temperature and then 1.63 g (7.7.mmole, 7 eq) sodium triacetoxyborohydride was added. The reaction mixture was stirred for twelve hours and filtered. The resin was washed three times with DMF, three times with dichloromethane, three times with methanol, and three times with dichloromethane.

[0022] The next step was performed by general solid phase synthesis. To a solution of 1.0 g resin and 1 ml DIEA in 50 ml anhydrous THF at room temperature, amino-mono-substituted triazine compounds of a mono-alkoxy-substituted triazine (4 eq) was added. The reaction mixture was stirred for two hours at 60°C and filtered. The resin was washed three times with DMF, three times with dichloromethane, three times with methanol, and three times with dichloromethane.

[0023] The final coupling step was performed by general solid phase synthesis. To the resin (10 mg) and 0.1 ml DIEA in 0.7 ml NMP was added 4 eq of each amine. The reaction mixture was stirred for two hours at 120°C and filtered. The resin was washed three times with DMF, three times with dichloromethane, three times with methanol, and three times with dichloromethane. Resin cleavage was conducted using 10% trifluoroacetic acid in dichloromethane for 30 minutes at room temperature, after which the resin was washed with dichloromethane. The products were identified using LC-MS ((Agilent 1100 model).

[0024] Figure 5 illustrates syntheses of triazine compounds with linker. In this Figure, the reagents are:

a. 2-[2-amino-ethoxy-ethoxymethyl]-carbamic *tert*-butyl ester, 2% acetic acid in DMF, room temperature, one hour

b. sodium triacetoxyborobutyride, room temperature, for twelve hours

c. 2,4-dichloro-6-morpholine-4-yl-[1,3,5]-triazine, DIEA, at 60°C for two hours

d. cyclopentylamine or benzylamine, DIEA,, at 120°C for two hours

e. 10% trifluoroacetic acid in dichloromethane for 30 minutes

[0025] Figure 1 illustrates examples of triazine-linker compounds. These examples are for purposes of illustration only, and are not intended to be limiting of the invention.

[0026] Table 2 illustrates compounds synthesized by the method of the present invention which were identified by LC-MS (Agilent 1100 model).

Table 2. Identification of Synthesized Compounds (with LC-MS).

The products were identified LC-MS (Agilent 1100 model).

R_2 \ R_1	A	B	C	D	E	F	G	H	I	J	K	L	M
0	347	317	331	471	411	319	385	347	345	401	333	381	367
1	433	403	417	557	497	405	471	433	431	487	419	467	453
2	502	472	486	626	566	474	540	502	500	556	488	536	522
3	486	456	470	610	550	458	524	486	484	540	472	520	506
4	368	338	352	492	432	340	406	368	366	422	354	402	388
5	422	392	406	546	486	394	460	422	420	476	408	456	442
6	444	414	428	568	508	416	482	444	442	498	430	478	464
7	419	389	403	543	483	391	457	419	417	473	405	453	439
8	419	389	403	543	483	391	457	419	417	473	405	453	439
9	436	406	420	560	500	408	474	436	434	490	422	470	456
10	522	492	506	646	586	494	560	522	520	576	508	556	542
11	418	388	402	542	482	390	456	418	416	472	404	452	438
12	497	467	481	621	561	469	535	497	495	551	483	531	517
13	384	354	368	508	448	356	422	384	382	438	370	418	404
14	440	410	424	564	504	412	478	440	438	494	426	474	460
15	384	354	368	508	448	356	422	384	382	438	370	418	404
16	474	444	458	598	538	446	512	474	472	528	460	508	494
17	452	422	436	576	516	424	490	452	450	506	438	486	472
18	382	352	366	506	446	354	420	382	380	436	368	416	402
19	424	394	408	548	488	396	462	424	422	478	410	458	444
20	424	394	408	548	488	396	462	424	422	478	410	458	444
21	410	380	394	534	474	382	448	410	408	464	396	444	430
22	438	408	422	562	502	410	476	438	436	492	424	472	458
23	396	366	380	520	460	368	434	396	394	450	382	430	416
24	508	478	492	632	572	480	546	508	506	562	494	542	528
25	478	448	462	602	542	450	516	478	476	532	464	512	498
26	478	448	462	602	542	450	516	478	476	532	464	512	498
27	398	368	382	522	462	370	436	398	396	452	384	432	418
28	436	406	420	560	500	408	474	436	434	490	422	470	456
29	436	406	420	560	500	408	474	436	434	490	422	470	456
30	436	406	420	560	500	408	474	436	434	490	422	470	456
31	398	368	382	522	462	370	436	398	396	452	384	432	418

32	370	340	354	494	434	342	408	370	368	424	356	404	390
33	448	418	432	572	512	420	486	448	446	502	434	482	468
34	448	418	432	572	512	420	486	448	446	502	434	482	468
35	462	432	446	586	526	434	500	462	460	516	448	496	482
36	432	402	416	556	496	404	470	432	430	486	418	466	452
37	432	402	416	556	496	404	470	432	430	486	418	466	452
38	424	394	408	548	488	396	462	424	422	478	410	458	444
39	424	394	408	548	488	396	462	424	422	478	410	458	444
40	424	394	408	548	488	396	462	424	422	478	410	458	444
41	398	368	382	522	462	370	436	398	396	452	384	432	418
42	518	488	502	642	582	490	556	518	516	572	504	552	538
43	440	410	424	564	504	412	478	440	438	494	426	474	460
44	432	402	416	556	496	404	470	432	430	486	418	466	452
45	396	366	380	520	460	368	434	396	394	450	382	430	416
46	462	432	446	586	526	434	500	462	460	516	448	496	482
47	383	353	367	507	447	355	421	383	381	437	369	417	403

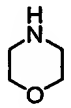
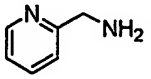
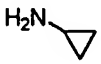
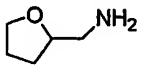
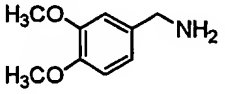
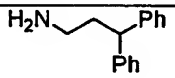
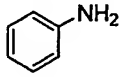
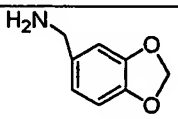
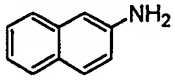
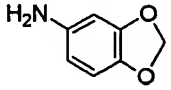
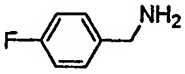
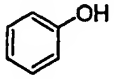
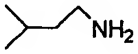
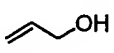
R_1 / R_2	N	O	P	Q	R	S	T	U	V	W	X	Y
0	368	361	427	353	403	397	354	318	320	444	334	292
1	454	447	513	439	489	483	440	404	406	530	420	378
2	523	516	582	508	558	552	509	473	475	599	489	447
3	507	500	566	492	542	536	493	457	459	583	473	431
4	389	382	448	374	424	418	375	339	341	465	355	313
5	443	436	502	428	478	472	429	393	395	519	409	367
6	465	458	524	450	500	494	451	415	417	541	431	389
7	440	433	499	425	475	469	426	390	392	516	406	364
8	440	433	499	425	475	469	426	390	392	516	406	364
9	457	450	516	442	492	486	443	407	409	533	423	381
10	543	536	602	528	578	572	529	493	495	619	509	467
11	439	432	498	424	474	468	425	389	391	515	405	363
12	518	511	577	503	553	547	504	468	470	594	484	442
13	405	398	464	390	440	434	391	355	357	481	371	329
14	461	454	520	446	496	490	447	411	413	537	427	385
15	405	398	464	390	440	434	391	355	357	481	371	329
16	495	488	554	480	530	524	481	445	447	571	461	419

17	473	466	532	458	508	502	459	423	425	549	439	397
18	403	396	462	388	438	432	389	353	355	479	369	327
19	445	438	504	430	480	474	431	395	397	521	411	369
20	445	438	504	430	480	474	431	395	397	521	411	369
21	431	424	490	416	466	460	417	381	383	507	397	355
22	459	452	518	444	494	488	445	409	411	535	425	383
23	417	410	476	402	452	446	403	367	369	493	383	341
24	529	522	588	514	564	558	515	479	481	605	495	453
25	499	492	558	484	534	528	485	449	451	575	465	423
26	499	492	558	484	534	528	485	449	451	575	465	423
27	419	412	478	404	454	448	405	369	371	495	385	343
28	457	450	516	442	492	486	443	407	409	533	423	381
29	457	450	516	442	492	486	443	407	409	533	423	381
30	457	450	516	442	492	486	443	407	409	533	423	381
31	419	412	478	404	454	448	405	369	371	495	385	343
32	391	384	450	376	426	420	377	341	343	467	357	315
33	469	462	528	454	504	498	455	419	421	545	435	393
34	469	462	528	454	504	498	455	419	421	545	435	393
35	483	476	542	468	518	512	469	433	435	559	449	407
36	453	446	512	438	488	482	439	403	405	529	419	377
37	453	446	512	438	488	482	439	403	405	529	419	377
38	445	438	504	430	480	474	431	395	397	521	411	369
39	445	438	504	430	480	474	431	395	397	521	411	369
40	445	438	504	430	480	474	431	395	397	521	411	369
41	419	412	478	404	454	448	405	369	371	495	385	343
42	539	532	598	524	574	568	525	489	491	615	505	463
43	461	454	520	446	496	490	447	411	413	537	427	385
44	453	446	512	438	488	482	439	403	405	529	419	377
45	417	410	476	402	452	446	403	367	369	493	383	341
46	483	476	542	468	518	512	469	433	435	559	449	407
47	404	397	463	389	439	433	390	354	356	480	370	328

[0027] Table 3 illustrates structures of R_1 groups in the triazine compounds produced according to the present

invention. These structures are for purposes of illustration only, and not for limitation.

Table 3. Structures of R_1 Group.

R_1	Structure	R_1	Structure
A		N	
B		O	
C		P	
D		Q	
E		R	
F		S	
G		T	
H		U	
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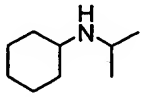
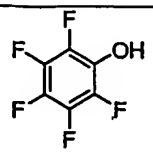
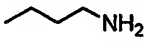
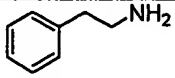
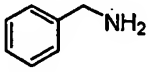
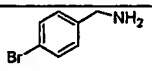
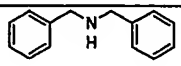
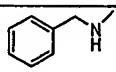
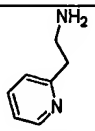
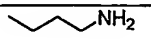
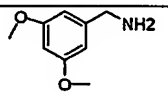
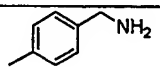
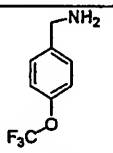
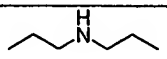
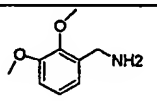
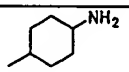
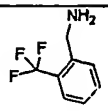
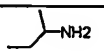
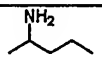
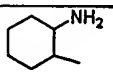
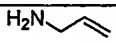
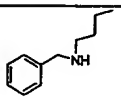
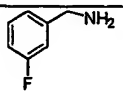
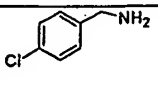
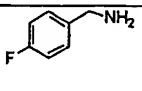
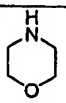
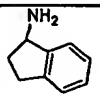
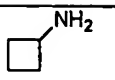
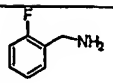
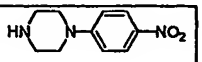
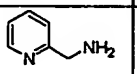
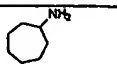
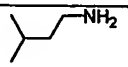
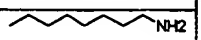
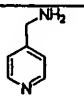
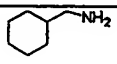
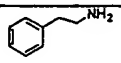
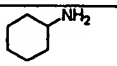
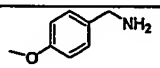
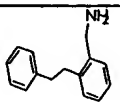
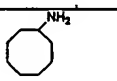
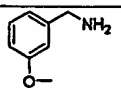
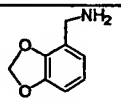
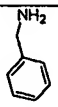
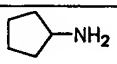
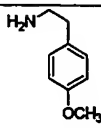
J		W	
K		X	
L		Y	CH_3OH
M			

Table 3. Structures of R_2 Group.

R_2	Structure	R_2	Structure	R_2	Structure	R_2	Structure
0	Cl	12		24		36	
1		13		25		37	
2		14		26		38	
3		15		27		39	
4		16		28		40	
5		17		29		41	

6		18		30		42	
7		19		31		43	
8		20		32		44	
9		21		33		45	
10		22		34		46	
11		23		35		47	

[0028] Generally, R_1 may be a C_{1-14} alcohol or amino group , a C_{1-14} alkyl group, phenyl substituted with at least one of F, Cl, methoxy, ethoxy, trifluoromethyl, or C_{1-6} alkyl; or benzyl substituted with at least one of F, Cl, methoxy, ethoxy, trifluoromethyl, or C_{1-6} alkyl. R_2 may be a C_{1-14} amino group , a C_{1-14} alkyl group, phenyl substituted with at least one of F, Cl, methoxy, ethoxy, trifluoromethyl, or C_{1-6} alkyl; or benzyl substituted with at least one of F, Cl, methoxy, ethoxy, trifluoromethyl, or C_{1-6} alkyl.

Agarose bead synthesis

[0029] In a 1 ml syringe cartridge (Ppcartridge with 20 m PE frit), 1 ml of Reacti-Gel 6X in acetone (purchased from Pierce), 10 ml of crosslinked agarose, 45-165 mm, >50 mmole/ml gel was added and 2 mL x 1 0.1 M K_2CO_3 Reacti-Gel 6X in a 3 mL syringe cartridge was suspended with 1 mL of 0.1 M K_2CO_3. To this was added 100 mL (50 mM) in DMSO) triazine-linker compound with amine. The coupling buffer was removed and Tris

buffer was added to block any excess reactive groups. The reaction mixture was washed twice with 10 mL H_2O and twice with 10 mL PBS.

Application of Triazine Linker Library and Affinity Matrices

[0030] The triazine linker library molecules can be used in a variety of phenotypic assays to find interesting small molecules and their binding proteins in an expeditious way. These assays include Zebrafish embryo development, morphological changes in S-pombi, membrane potential sensing in cell systems, phenotypic screening in C-elenas, muscle regeneration in newt, tumorigenesis in brain cells, apoptosis and differentiation of cancer cells, cell migration and anti-angiogenesis. The active compounds are classified depending upon their ability to induce unique morphological changes, and these are then used for affinity matrix work.

[0031] Selected linker library molecules are loaded onto activated agarose beads via their amino-end linkers as described above. These affinity matrix beads are incubated with cell or tissue extract, and found proteins run on gel. The found proteins are analyzed using MS-MS sequencing after in-gel digestion to give the peptide sequences of the target protein.

[0032] The linker library molecules can be used for making a high density small molecule chip. Thousands of linker library molecules are immobilized on a glass slide by a spotting method, which can add hundreds to thousands or molecules to a slide. The amino end of the linker is connected to an activated functional group on the slide, such as isocyanate, isothiocyanate, or acyl imidazole. Fluorescent labeled proteins with different dyes are incubated with the slide. A scanner analyzes the color to give the absolute and relative binding affinity of different proteins on each compound. For example, no color means there is no activity with any kind of proteins. A strong mixed color means that

the compounds are non-specifically active with multiple proteins. Exclusively stained compounds, with a singe color, indicate a selective bind of the relevant protein. Using this technique, thousands of small molecules can be tested in a shot time using a small amount of protein. In this approach, limited numbers of purified proteins compete with each other in the presence of multiple small molecules. This approach is analogous to DNA microarray technology, which has been important in advances in functional genomics. Although there have been some reports of protein chips 8, at yet no small molecule library chip has been demonstrated. Therefore, the small molecule chips of the present invention will offer totally new techniques in the field of chemical genetics, which will expand the study of the entire genome.

[0033] Thus the present invention dramatically accelerates chemical genetics techniques by connecting phenotypic assay and affinity matrix work without any delay, rather than requiring months to year of SAR work. This powerful technique will revolutionize the study of the genome and will open a new field of chemical proteomics. Combining the binding protein data with a phenotype index will serve as a general reference of chemical knock-out. The present invention makes it possible to identify novel protein targets for drug development as well as drug candidates.

[0034] The foregoing description of the specific embodiments will so fully reveal the general nature of the invention that others can, by applying current knowledge, readily modify and/or adapt for various applications such specific embodiments without departing from the generic concept, and, therefore, such adaptions and modifications should and are intended to be comprehended within the meaning and range of equivalents of the disclosed embodiments. It is to be understood that the phraseology or terminology employed

herein is for the purpose of description and not of limitation.

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WHAT IS CLAIMED IS:

1. A trisubstituted triazine library.

2. A method for preparing a trisubstituted triazine library comprising:

a. making a first building block by adding a first amine by reductive amination of triazine;

b. making a second building block by adding a second amine to cyanuric chloride;

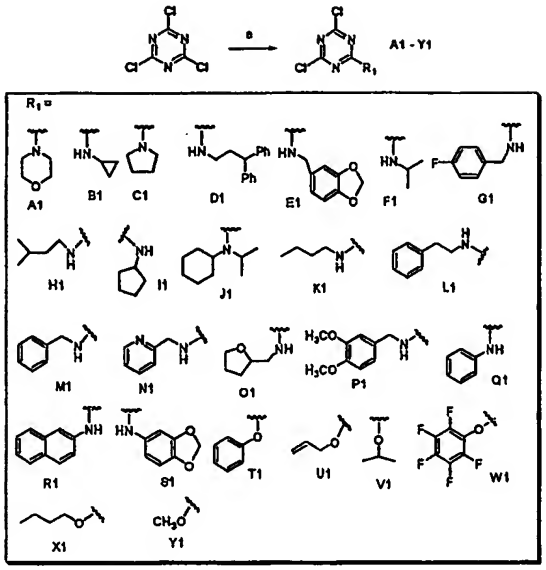
c. combining said first building block with said second building block by aminating the first building block onto one of the chloride positions of the second building block;

d. reacting a third building block with the combined first and second building blocks to produce a trisubstituted triazine.

3. The process according to claim 2 wherein the first amine is selected from the group consisting of amines substituted with at least one of a C_{1-14} alcohol or amino group, a C_{1-14} alkyl group, phenyl substituted with at least one of F, Cl, methoxy, ethoxy, trifluoromethyl, and C_{1-6} alkyl; and benzyl substituted with at least one of F, Cl, methoxy, ethoxy, trifluoromethyl, and C_{1-6} alkyl; and the second amine is substituted with at least one of a C_{1-14} amino group , a C_{1-14} alkyl group, phenyl substituted with at least one of F, Cl, methoxy, ethoxy, trifluoromethyl, and C_{1-6} alkyl; and benzyl substituted with at least one of F, Cl, methoxy, ethoxy, trifluoromethyl, and C_{1-6} alkyl.

4. The process according to claim 2 wherein the first building block is selected from compounds of the formula:

wherein R_1 is selected from the group consisting of

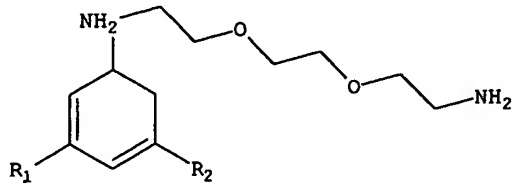


5. A process for synthesizing a triazine library with linker comprising reacting a trisubstituted triazine according to claim 1 with a linker.

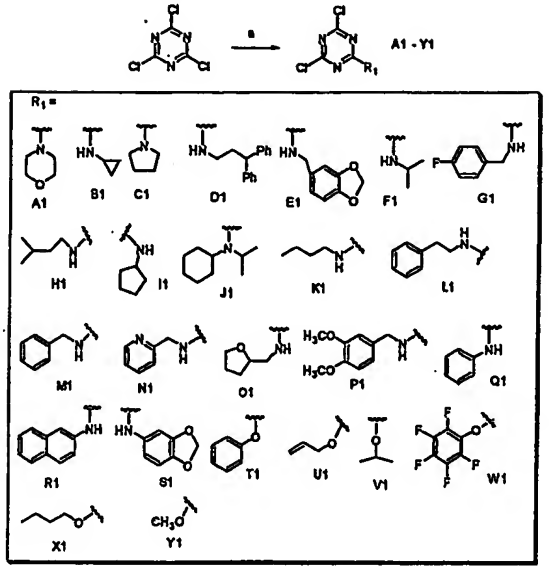
6. The process according to claim 5 wherein the linker is 2-[2-amino-ethoxy-ethyoxyethyl]carbamic *tert*-butyl ester.

7. Triazine-linker compounds comprising a trisubstituted triazine bonded to a linker.

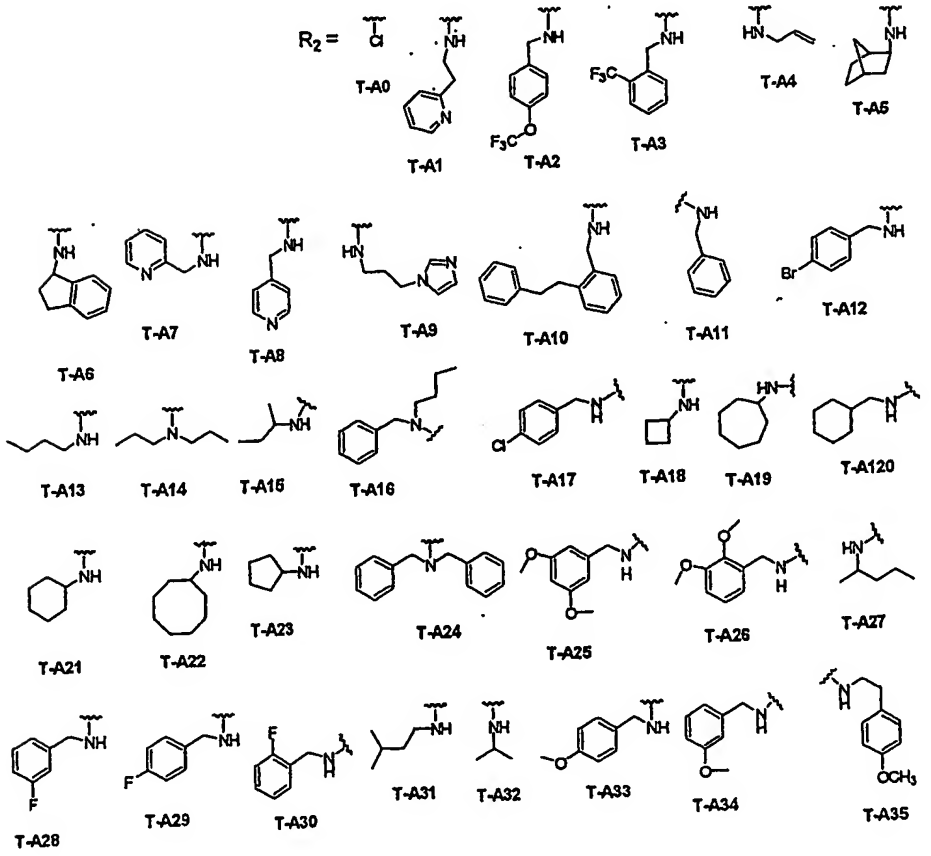
8. The compounds according to claim 7 selected from compounds of the following formula:

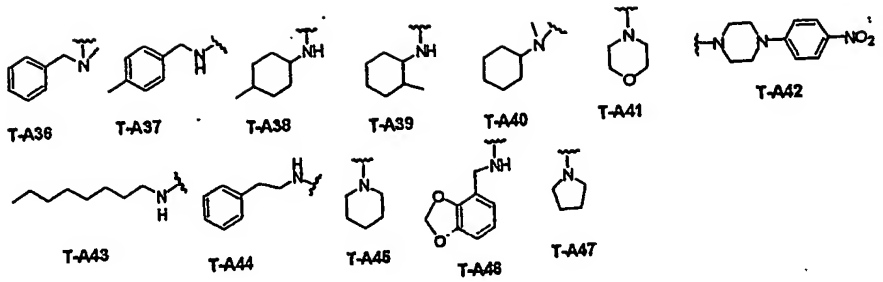


wherein R_1 is selected from the group consisting of



wherein R_2 is selected from the group consisting of





9. Affinity matrix beads comprising a triazine linker compound according to claim 7 loaded onto activated beads.

10. The affinity matrix beads according to claim 9 wherein the beads are agarose.

11. A high density small molecule chip comprising a surface onto which are linked triazine linker compounds according to claim 7.

12. The high density small molecule chip according to claim 11 wherein the surface is a glass slide.

13. The high density small molecule chip according to claim 11 wherein the amino end of the linker is connected to an activated functional group on the surface.

14. The high density small molecule chip according to claim 13 wherein the activated functional group is selected from the group consisting of isocyanate, isothiocyanate, and acyl imidazole.

15. A method for determining the binding affinity of proteins to a plurality of molecules comprising incubating

a high density small molecule chip according to claim 11 with a plurality of labeled proteins, and analyzing the labels to determine which molecule have affinity for which proteins.

16. The method according to claim 15 wherein the label is a florescent label.

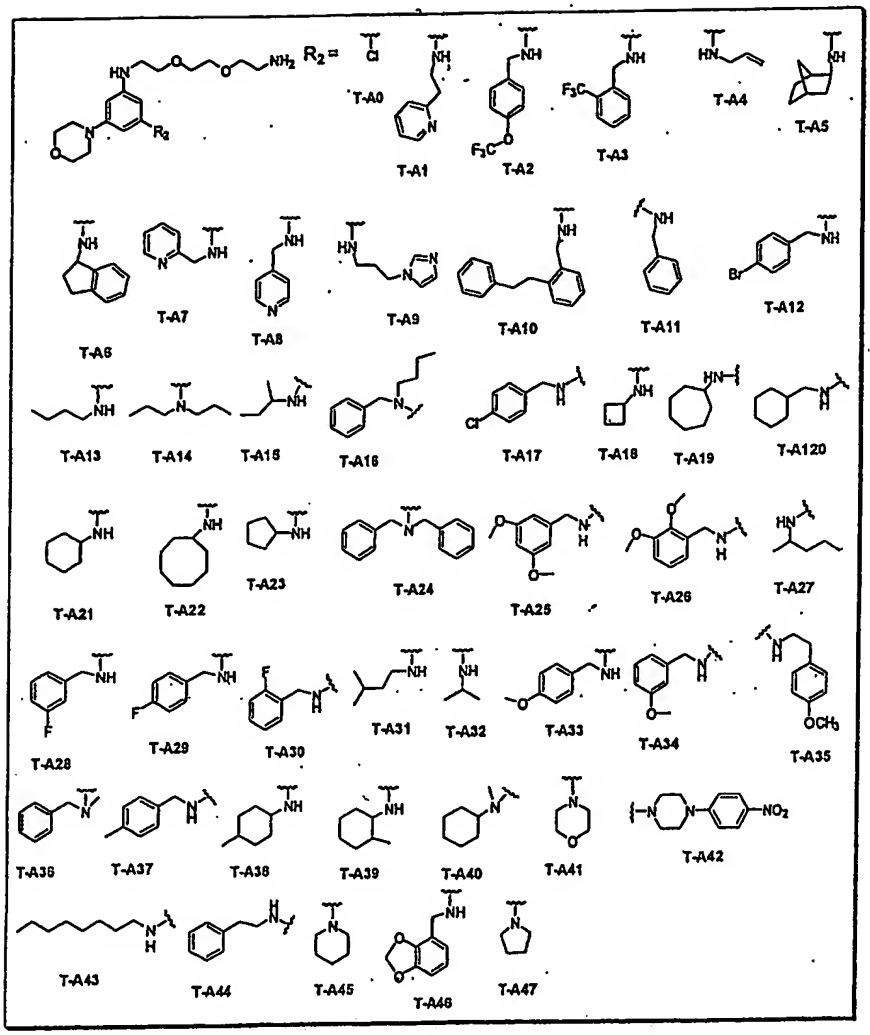


FIGURE 1

Examples of triazine-linker compounds

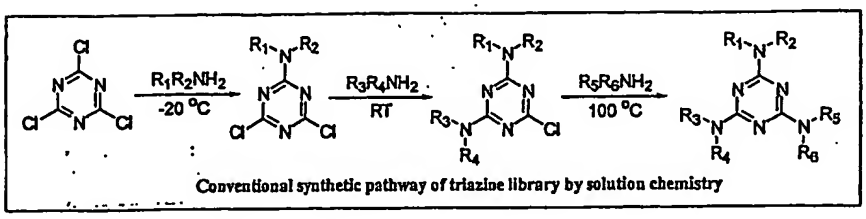


FIGURE 2

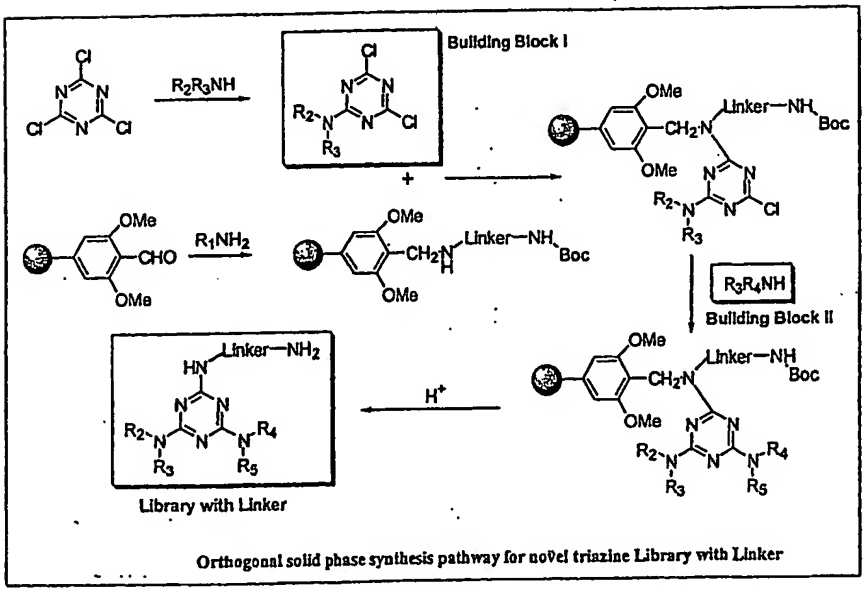
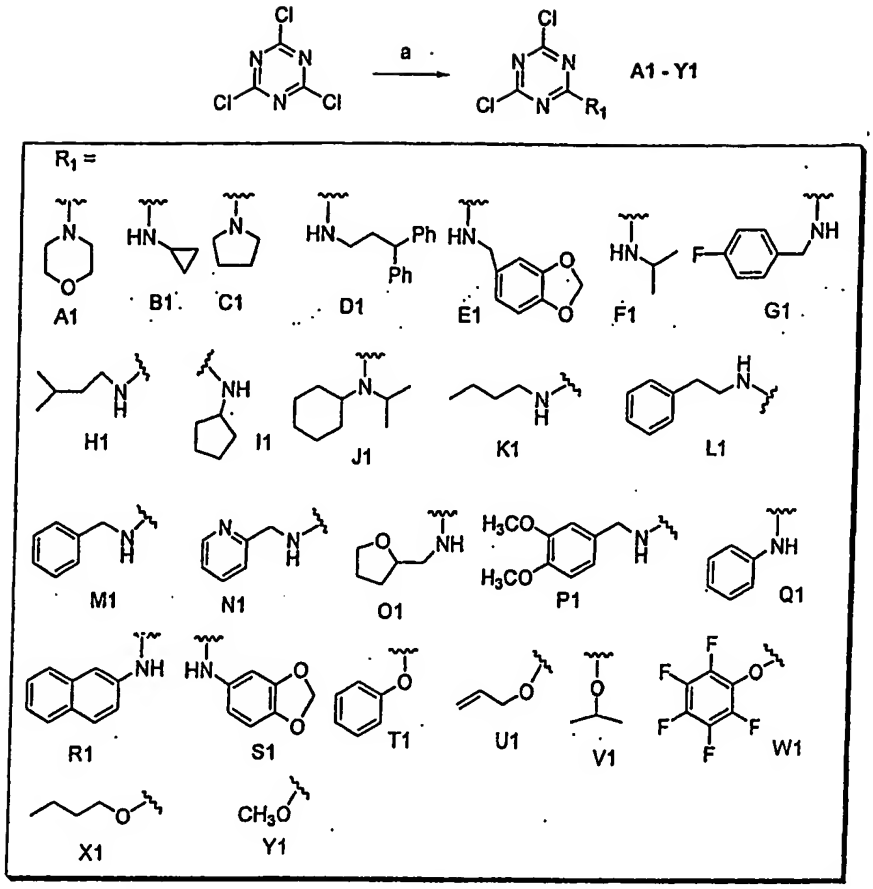
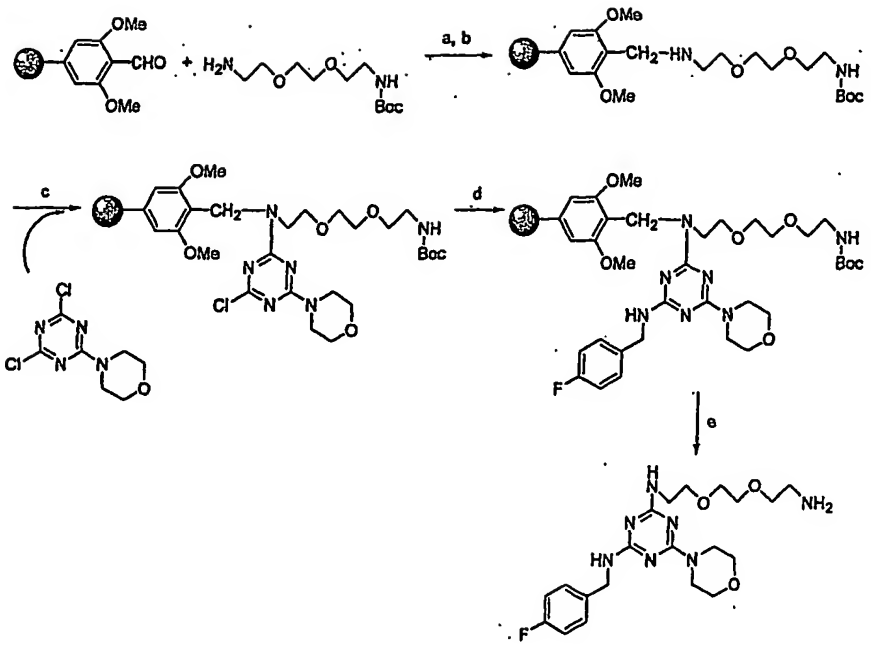


FIGURE 3



Reagents: (a) each amines, 30 min, 0 °C.

FIGURE 4



Reagents: (a) 2-[2-amino-ethoxy-ethoxymethyl]-carbamic *tert*-butyl ester, 2 % acetic acid in DMF, rt, 1hr. (b) Sodium triacetoxyborohydride, rt, 12 hr. (c) 2,4-Dichloro-6-morpholine-4-yl-[1,3,5]triazine, DIEA, 60 °C, 2 hr. (d) Cyclopentylamine or benzylamine, DIEA, 120 °C, 2 hr. (e) 10% Trifluoroacetic acid in dichloromethane, 30 min.

FIGURE 5

Syntheses of triazine compound with linker.

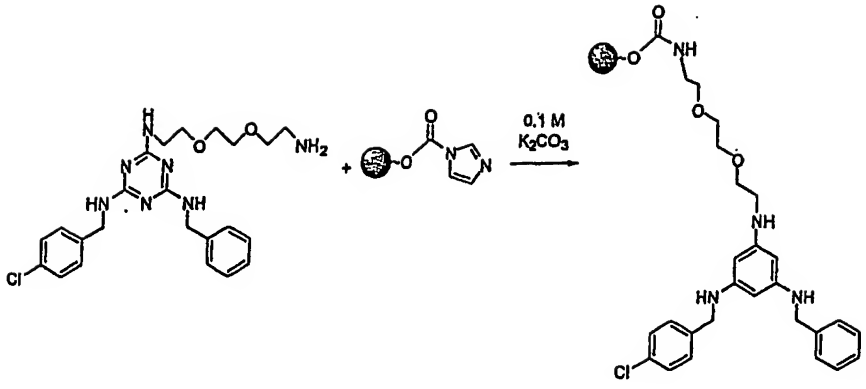


FIGURE 6